Treatment of Hyperkinetic Movement Disorders with Tetrabenazine: A Double-blind Crossover Study

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Tetrabenazine, a presynaptic monoamine depleting agent, has been reported to have an ameliorating effect in a variety of hyperkinetic movement disorders. In a double-blind crossover trial of tetrabenazine versus placebo, 19 patients with a variety of hyperkinetic movement disorders were evaluated. During the evaluation period, all but 4 patients were treated for three or more weeks at a maximum dosage of 200 mg per day. The patients were examined and rated using clinical assessment of hyperkinesia, and movies of their activities were randomized and rated by an independent group of neurologists. A good correlation was found between the clinical examination scale and the film analysis score. Improvement was seen in all 4 patients with tardive dyskinesia, 4 of 6 patients with Meige disease, and 5 of 6 patients with other dystonias. One patient with Huntington disease showed marked improvement and 2 patients with congenital choreoathetosis showed only mild improvement. The most frequent side effects included daytime drowsiness, drooling or sialorrhea, insomnia, restlessness and anxiety, parkinsonian features, and mild postural hypotension. The adverse effects resolved with continued administration or with reduction in dosage. Tetrabenazine is a useful and safe therapeutic agent in some patients with hyperkinetic movement disorders.

Jankovic J: Treatment of hyperkinetic movement disorders with tetrabenazine: a double-blind crossover study. Ann Neurol 11:41–47, 1982

Hyperkinetic movement disorders are characterized by excessive involuntary movements. The movements may be repetitive and stereotyped, such as tremor, dystonia, ballism, tics, akathisia, and a variety of sporadic or drug-induced dyskinesias, or may be quite unpredictable and unpatterned, such as chorea, athetosis, and myoclonus. Although generally useful, this clinical classification often makes atypical disorders difficult to classify. The biochemical, pharmacological, and neurophysiological information presently available is insufficient to be of practical value in differentiating the various kinds of movement disorders.

It has been suggested that some of the hyperkinetic disorders, particularly chorea and tardive dyskinesia, are associated with central monoamine overactivity or relative central cholinergic deficiency. Therefore, drugs that are dopaminergic, such as levodopa, bromocriptine, and amphetamines, may exacerbate certain hyperkinesias. Conversely, drugs that inhibit catecholamine synthesis (α-methyl-L-tyrosine), block dopamine receptors (phenothiazines and butyrophenones), deplete brain monoamines (reserpine and tetrabenazine), or increase central cholinergic effect (physostigmine, choline, and lecithin) may suppress abnormal involuntary movements.

A monoamine depleting drug, tetrabenazine, has been reported to be of benefit in the treatment of a variety of hyperkinesias [1, 9–11, 22, 23, 26, 27, 29]. McLellan et al [20], comparing tetrabenazine to thiopropazine and placebo, concluded that "tetrabenazine is the drug of first choice for the suppression of chorea in patients with Huntington's chorea." Although such statements should be interpreted cautiously, subsequent experience in Europe and more recently in the United States has been encouraging. With few exceptions [9, 20], almost all previous reports were based on open trials or anecdotal observations.

The results of a prospective double-blind crossover trial of tetrabenazine versus placebo in a variety of hyperkinetic movement disorders are reported. This study indicates that tetrabenazine is a useful and safe therapeutic agent in certain hyperkinesias.

Patients and Methods

Twenty patients, 9 male and 11 female, aged 8 through 80 years, were studied (Table 1). Six patients had Meige disease (sporadic-onset blepharospasm and oromandibular

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Received Feb 23, 1981, and in revised form Apr 13. Accepted for publication Apr 18, 1981.

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Table 1. Clinical Features

Patient No., Age (yr), and Sex	Diagnosis	Daily Dose (mg)	Duration of Treatment (wk)	Side Effects
1. 45, M	TD	200	3	Restlessness
2. 64, F	TD	200	6	None
3. 80, F	TD	200	5	Drooling, slowness, unsteadiness of gait
4. 68, F	TD	200	2	Mild parkinsonism
5. 49, F	Meige	175	5	Anxiety
6. 51, F	Meige	200	5	Tremulous drowsiness
7. 44, M	Meige	200	4	None
8. 63, M	Meige	200	1	Diarrhea, epigastric pain, right hand tremor, parkinsonism
9. 53, F	Meige	200	1	None
10. 62, F	Meige	100	3	Insomnia, fatigability, drooling, myalgia, muscle twitching
11. 49, M	Torticollis	75	5	Insomnia, drowsiness, fatigability, impotence
12. 57, M	Torsion dystonia, spasmodic dysphonia, essential tremor	200	6	Insomnia, tremor, sialorrhea, slowness
13. 23, F	Tardive dystonia	200	3	Drowsiness
14. 13, M	Dystonia-tic	50	4	Oculogyric crises, postural hypotension
15. 40, F	Torsion dystonia, S/P right thalamotomy	200	7	None
16. 8, M	Dystonia musculorum deformans (autosomal dominant)	150	4	Drowsiness, depression
17. 34, F	Huntington disease	200	10	None
18. 24, M	Dystonic choreoathetosis	100	5	Sialorrhea, drowsiness, hypotension
19. 41, M	Dystonic choreoathetosis	200	7	None

TD = tardive dyskinesia; S/P = status post.

dystonia), 4 had tardive dyskinesia, 3 had adult-onset dystonia, 2 had dystonic choreoathetosis associated with static encephalopathy, and 1 patient each had tardive dystonia, childhood-onset dystonia and tic, adult-onset dystonia and spasmodic dysphonia, severe autosomal dominant dystonia musculorum deformans, and Huntington disease. The nature and purpose of the study were explained to the patients and their next of kin, and a consent form listing potential side effects was signed by the patient or relative.

The patients were initially admitted to the General Clinical Research Center or the Neurosensory Center of Houston. After initial medical and neurological evaluation, laboratory studies were performed to exclude serious hematological, renal, hepatic, or cardiac problems. All medications were either discontinued one week before the study or continued at the same dosage throughout the study. Patients were randomly assigned into placebo or tetrabenazine groups. The drugs were administered orally as white tablets containing either 25 mg of tetrabenazine or placebo, and the dosage was gradually increased by one tablet every day to a maximum tolerated dose not exceeding 200 mg per day. The investigator was unaware of the identity of the pills, which was not revealed until after completion of the trial. After an average of 10 days of hospitalization, the patients were discharged and followed as outpatients every two to three weeks. They were readmitted for the second phase of the study, crossed over to an alternate form of therapy, and, after one week, were discharged to be followed again as outpatients. Each phase of the study lasted approximately six weeks. If side effects developed, the dose was not increased; if necessary, the dose was reduced until side effects were no longer bothersome. If a patient requested to remain on tetrabenazine at the completion of the study, the dosage was then adjusted according to the patient's needs and he or she continued to be followed at regular intervals in the Movement Disorder Clinic.

At the beginning of the trial and at the end of each phase, all patients were examined and after 30 minutes of observation the movement disorder was rated on a hyperkinesia scale (Table 2). Each sign was scored from 0 to 4 in direct proportion to its severity. While the patient was hospitalized and during subsequent evaluations, relatives, nurses, and other physicians were invited to comment on

Table 2. Hyperkinesia Signs and Rating Scale

Oral-lingual-facial Hyperkinesia
Frontalis contraction
Eye blinking (blepharospasm)
Upper lip tremor (rabbit syndrome)
Lip pouting, puckering
Lip smacking, licking
Chewing movements
Jaw opening
Tongue protrusion—voluntary
Tongue protrusion-retraction (darting or fly-catcher's tongue)
Bon-bon sign
Facial tics
Vocalization—grunting
Palatopharyngeal (choking) spasms
Speech
Other
Upper Limb Hyperkinesia
Dystonia—proximal, distal (writer's cramp)
Ballistic movements
Choreoathetoid movements—fingers, wrists, proximal
Milkmaid grip—contraction tremor
Tremor at rest—supination/pronation or flexion/extension
Sustention tremor
Intention tremor
Rapid succession movements
Handwriting
Other
Neck and Trunk Hyperkinesia
Respiratory dyskinesia
Platysmal contractions
Shoulder shrugging
Head tremor (negation/affirmation)
Torticollis to right vs. left
Retrocollis
Truncal dystonia
Truncal rocking—titubation
Pelvic thrusting
Other
Lower Limb Hyperkinesia
Foot dystonia
Toe movements
Marching in place—standing
Stamping movements—sitting
Restless legs—akathisia
Crossing/uncrossing legs
Shuffling gait
Ataxic gait
Rapid succession movements
Other
0–4 Rating Scale
0 = Absent
1 = Mild, hardly noticeable
2 = Moderate, definitely present but does not interfere with functional activity
3 = Severe, interferes with patient's function
4 = Very severe, incapacitating

the patient's condition, and their impressions were recorded. Patients were specifically questioned regarding any possible side effects.

At the conclusion of each clinical examination, the patients were filmed in standardized postures and performing standard tests. The films were then randomized, and a group of six board-certified neurologists reviewed and scored each film on a scale of 0 to 10.

Results

Clinical Assessment

The clinical features, tetrabenazine dose, duration of treatment, and side effects are shown in Table 1, and Figure 1 summarizes the clinical results. When the group was analyzed as a whole, this double-blind study demonstrated significant reduction in involuntary movements during the tetrabenazine versus the placebo phase ($p < 0.005$ by the Wilcoxon Matched-Pairs Signed-Ranks test). All 4 patients with tardive dyskinesia improved during the tetrabenazine phase. Among the 6 patients with Meige disease, 4 showed definite improvement, Patient 8 worsened, and Patient 7 showed no change. This last patient, when placed on carbidopa and levodopa (Sinemet), showed marked improvement; he was able to return to full employment after two months of total disability, and his blepharospasm and oromandibular dystonia disappeared almost completely. Patient 8 was unable to tolerate tetrabenazine; because of diarrhea, epigastric pain, and parkinsonian features, the medication was discontinued after one week at a dosage of 200 mg per day. This is the only patient in the study whose movement disorder worsened with tetrabenazine because of emergence of parkinsonian signs. Patient 10 experienced marked side effects including insomnia, fatigue, drooling, muscle tenderness, and fasciculations when the dosage was advanced to 200 mg per day, but side effects cleared with reduction of the dosage to 100 mg per day. In 7 patients dystonia was the predominant movement disorder, and some improvement occurred during the period of observation (3 to 7 weeks) in all of them except Patient 12, who had anterocollis, torticollis, spasmodic dysphonia, and essential tremor. However, after completion of the double-blind protocol, this patient had the tetrabenazine dosage increased from 200 to 300 mg per day and the spasmodic dysphonia improved greatly. His voice remained normal for approximately 60% of the time, whereas before the increase in dosage the spasmodic dysphonia was constant. In 1 patient with adult-onset torsion dystonia, moderate daytime restlessness developed on the first day of tetrabenazine therapy and the patient asked to be removed from the study. Two patients with lifelong dystonic choreoathetosis due to static encephalopathy had mild improvement. The patient with Huntington chorea improved moder-

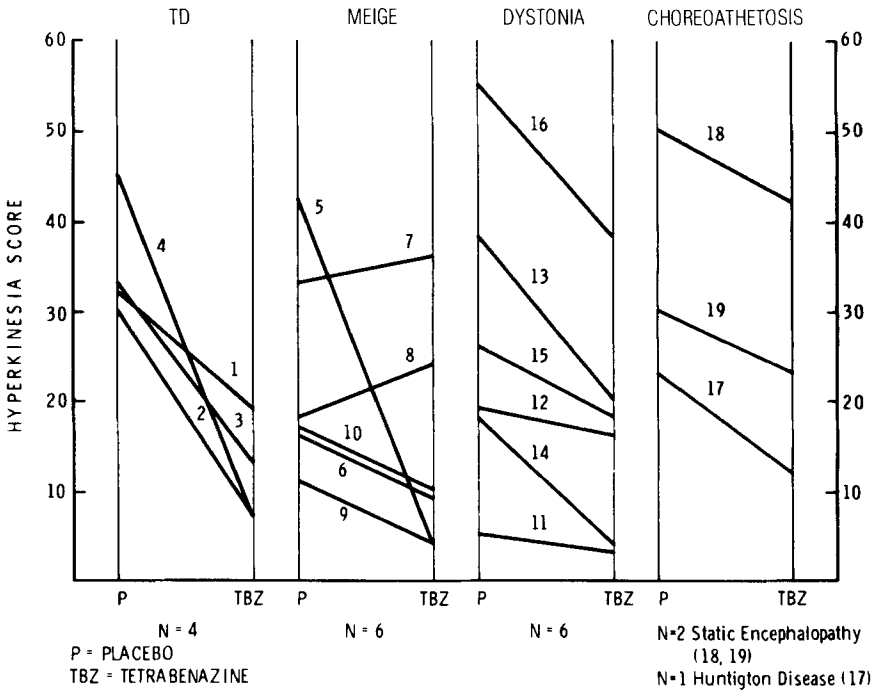

Fig 1. Tetrabenazine therapeutic response. Clinical assessment. (Numbers are patient numbers; see Table 1.)

ately but, because of poor compliance, tetrabenazine was discontinued after 10 days.

Film Analysis

The results of film analysis are shown in Figure 2. An excellent correlation was found between the clinical assessment and film analysis score. The only discrepancies were in Patient 7, in whom clinical assessment suggested mild deterioration and film analysis score indicated mild improvement, and Patient 12, in whom the reverse situation occurred. In both patients the change as indicated by either score was small and insignificant. Because of technical difficulties, video recording of Patients 11 and 16 was not possible. In Figure 2 the hyperkinesia score represents a sum of individual scores as rated by the six neurologists.

Discussion

First marketed in Switzerland in 1959, tetrabenazine has been used as a tranquilizer under the trade name of Nitoman. Because of its monoamine depleting action [24], several investigators have suggested that this benzoquinolizine derivative may be useful in the symptomatic treatment of chorea [1, 20, 26, 29], athetosis [9], spontaneous [22] and tardive orofacial dyskinesia [1, 11], ballism [23, 26], dystonia [1, 26, 29], tics [27], and segmental myoclonus [10]. This conclusion is supported by the results of our double-blind crossover trial showing improvement in hyperkinesia score with tetrabenazine versus placebo ($p < 0.005$ by the Wilcoxon Matched-Pairs Signed-Ranks test). All 4 patients with tardive dyskinesia, 4 of 6 with Meige disease, 5 of 6 with other dystonias, and 1 with Huntington disease improved. Two patients with dystonic choreoathetosis associated with static encephalopathy showed only mild improvement.

Although any clinical evaluation method has some limitations, the multiple-sign hyperkinesia scale used in the clinical assessment appears reliable, and, when only one rater is used, the scores are usually consistent from one evaluation to another. In the film assessment there was no or only minimal variability among the different reviewers. The double-blind technique, however, is essential for objectivity in the evaluation of therapy in movement disorders. In this study the patients were not preselected in any way except that most were referred because they had failed to respond to various forms of therapy. Their condition had remained unchanged for months to years before the study and during the placebo phase. Therefore, any lasting change in the movement disorder was most likely due to the pharmacological treatment. In addition to demonstrating reduction in their involuntary movements, most patients also reported functional improvement, although this is difficult to assess by any quantitative method.

The pathogenetic mechanisms of the various involuntary movement disorders are poorly understood, but it has been suggested that central monoaminergic preponderance may play an impor-

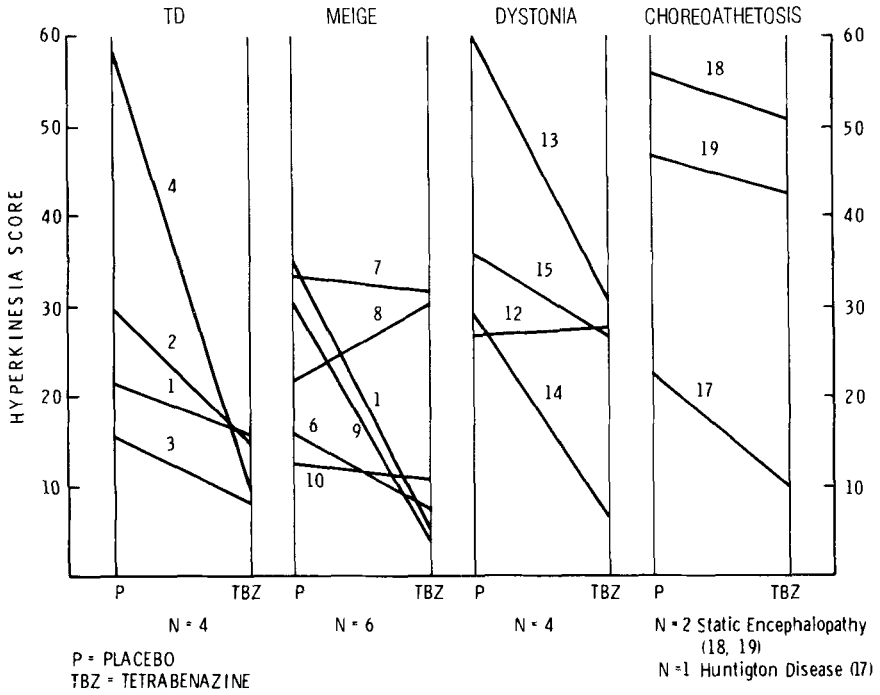

Fig 2. Tetrabenazine therapeutic response. Film assessment. (Numbers are patient numbers; see Table 1.)

tant role in many hyperkinetic movement disorders. In tardive dyskinesia, for example, as a result of chronic dopamine receptor blockade, a compensatory receptor site hypersensitivity or an increase in synthesis of postsynaptic dopamine receptors may occur [6, 7]. In Meige disease, dopaminergic preponderance has been suggested as a possible mechanism [30]. In Huntington chorea, dopaminergic drugs (levodopa, bromocriptine) exacerbate the choreatic movements, whereas dopamine blocking agents (haloperidol) and dopamine depleting agents (tetrabenazine) ameliorate the involuntary movements, suggesting relative dopaminergic preponderance [2, 14]. Dystonia is one of the least understood of all movement disorders. The finding of diminished homovanillic acid in ventricular fluid [28] and an elevation of plasma dopamine-β-hydroxylase in some patients with autosomal dominant torsion dystonia provides fragmentary evidence for biochemical abnormality in dystonia, but how these changes are related to the pathogenesis of dystonia is unclear [33]. Korczyn [15] suggested increased norepinephrine release as a possible biochemical abnormality in dystonia. This and other data suggest that catecholamine depleting agents such as tetrabenazine should be effective in reducing excessive involuntary activity in patients with hyperkinetic movement disorders.

Although some studies [12] have suggested that tetrabenazine exerts only a slight effect on depletion of serotonin, more recent data indicate that the depleting effect of tetrabenazine equally affects all three of the major neurotransmitters (dopamine, norepinephrine, and serotonin) and to a lesser extent reduces the level of acetylcholine, aspartate, glutamate, and possibly other putative neurotransmitters [18]. The depletion of norepinephrine and dopamine from the brainstem in rats by tetrabenazine has been correlated with reduction in spontaneous exploratory behavior [5]. In humans, parkinsonian features, particularly tremor, appear to be related to antidopaminergic action [3, 17]. These tetrabenazine-induced effects may be antagonized by tricyclic antidepressants, monoamine oxidase inhibitors, anticholinergics, amphetamines, and phenytoin [19].

The mechanism of action of tetrabenazine appears to be slightly different from that of reserpine, although the two drugs are similar in their depleting effects. Studying catecholamine-induced histofluorescence in ligated peripheral nerve preparations, Dahlström [8] and Tomlinson et al [31, 32] concluded that tetrabenazine causes reversible depletion, whereas reserpine binds irreversibly to the storage granules. Upon withdrawal of tetrabenazine, the intact storage granules are able to participate in the synthesis and storage of monoamines, whereas after treatment with reserpine, new storage granules must be synthesized in the cell body and transported down the axon into the nerve terminal. This may explain why tetrabenazine is a relatively short-acting agent compared to reserpine. Measuring synaptosomal conversion of tyrosine to dopamine as an index of dopamine synthesis, Kuczenski [16] sug-

Table 3. Side Effects of Tetrabenazine

Present Study	Other Reported Side Effects
Drowsiness (5)	Confusion
Sialorrhea—drooling (4)	Nausea
Insomnia (3)	Dysphagia
Restlessness and anxiety (3)	Hiccough
Slowness (3)	Blepharospasm
Tremor (3)	Photophobia
Fatigability (2)	Akathisia
Postural hypotension (2)	Myoclonus
Depression (1)	Shivering
Ataxia (1)	Diaphoresis
Diarrhea (1)	Pallor
Epigastric pain (1)	Transient fever
Impotence (1)	Tongue paresthesias
Myalgias and fasciculations (1)	Elevated lactic dehydrogenase
Oculogyric crises (1)	

Numbers in parentheses are number of patients in our study experiencing the side effect.

gested that tetrabenazine and reserpine have different effects on the nerve ending pool. Tetrabenazine apparently causes depletion of the storage as well as the functional pool, whereas reserpine primarily affects the storage pool. These studies require further elucidation and confirmation.

The two depleting agents, tetrabenazine and reserpine, also differ slightly in some pharmacological and clinical effects [4, 21, 25]. For instance, postural hypotension and depression appear to be less frequent with tetrabenazine; also, that drug's onset of action is more rapid. The differential clinical effect is illustrated by our Patient 4, with severe tardive dyskinesia, who was treated with a high dose of reserpine (4.5 mg per day) at which time she began to develop postural hypotension with no change in her dyskinesia. Within 24 hours of beginning tetrabenazine therapy, she showed marked improvement in her dyskinesia and this continued as long as tetrabenazine therapy lasted.

In summary, our double-blind crossover study supports the findings of previous open trials of tetrabenazine in a variety of hyperkinetic movement disorders. The drug appears to be a relatively safe and efficacious agent in some patients with involuntary movement disorders, particularly those with Huntington chorea and tardive dyskinesia. However, some patients with dystonia or Meige disease also respond. The most frequent side effects include drowsiness, sialorrhea and drooling, restlessness, anxiety, insomnia, parkinsonian features, and postural hypotension [13] (Table 3). All these side effects usually disappear when the drug is maintained at the same dose or when the dosage is reduced. Unfortunately, the favorable effects of tetrabenazine often decline or disappear after a few days or weeks of therapy [11]. In patients with long follow-up, intermittent therapy was noted to be an effective way of preventing this wearing-off effect. Empirically, one week on and two days off the regimen has been found useful in prolonging the favorable response to tetrabenazine, but this approach must be individualized and further studies are required to substantiate this clinical observation.

It is obvious that tetrabenazine treatment of hyperkinetic movement disorders is not ideal. However, until we advance in our knowledge of possible biochemical mechanisms of the various hyperkinesias, the treatment of these disorders will remain largely empirical. In contrast to dopamine blocking agents such as haloperidol, tetrabenazine does not appear to have serious long-lasting side effects such as tardive dyskinesia, and, as discussed, it offers certain advantages over reserpine. Since tetrabenazine is not readily available, reserpine (with or without α-methyltyrosine) remains a practical alternative to tetrabenazine in the treatment of chorea and tardive dyskinesia.

I thank my colleagues, Drs Ashizawa, Armstrong, Derman, Elias, Harati, and Strittmatter, for their assistance with film evaluation. Lynn Evans, PhD, of the Department of Community Medicine at Baylor College of Medicine, helped with statistical analysis. The patients were evaluated in the General Clinical Research Center of the Methodist Hospital and Baylor College of Medicine. Tetrabenazine and placebo were generously supplied by Hoffmann-La Roche Inc, Nutley, NJ.

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